

**REMARKS:**

Claim 1-5 are in the case and presented for consideration.

**Rejection Under 35 U.S.C. § 112**

Claims 1-5 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The reasons for the rejection are stated on page 2 of the Office Action. The rejection is respectfully traversed.

Claims 1-5 have been amended to recite "wherein" instead of "characterized in that", as suggested in the Office Action, to overcome the indefiniteness rejection under 35 U.S.C. § 112, second paragraph. Claim 1 has also been amended to recite "preparation of" instead of "manufacturing of", as suggested in the Office Action, to overcome the indefiniteness rejection under 35 U.S.C. § 112, second paragraph. Accordingly, the above grounds of rejection are believed to be moot.

It is further suggested in the Office Action that "a polar aprotic solvent" should be deleted since the specification teaches using only acetonitrile and since "there is no mention of any other polar aprotic solvent besides acetonitrile." Applicant respectfully maintains that describing an invention in terms of its exemplary embodiment does not form a basis for doubting the definiteness of the claim terms, i.e., "polar aprotic solvent" in this case.

The definiteness requirement of § 112, second paragraph, is satisfied if a person skilled in the field of the invention would reasonably understand the claim when read in the context of the specification. See *Marley Mouldings Ltd. v. Mikron Industries, Inc.*, 417 F.3d 1356, 1359 (Fed. Cir. 2005).

It is well known to one of ordinary skill in the art that solvents, if appropriately used, can influence the course of the chemical reactions in a required sense. This influence is not chemically specific, i.e., is not dependent on a specific chemical structure of a given solvent since the solvent does not act as reaction component (as opposed to the reaction components, the solvent does not take part in reaction and remains unchanged when the reaction is over), but is systemic which means that the mentioned influence is dependent

on that how the solvents behave towards the protons (which are aprotic or not) and how polar the solvents are (which are polar or not). These two properties of the solvents are crucial in influencing the course of chemical reactions, which substantially means that for two or more solvents being similarly aprotic and polar it could be, with high rate of probability, expected that all these aprotic polar solvents are able to influence a given reaction in the same way. In this sense, the aprotic polar solvents are in fact replaceable with one another. This rule or principle is generally known in the field of Applicant's invention.

Applicant has exemplified the claimed method of the present application using acetonitrile which is a typical representative of aprotic polar solvents. See, for instance, the well known Kolthoff's system of classification of solvents at <http://www.nap.edu/readingroom/books/biomems/ikolthoff.html> where it is mentioned, in paragraph 8, entitled "Chemistry of non-aqueous solutions", that "these studies were followed by a long series of investigations of a broad spectrum of solute-solvent interactions in various dipolar aprotic solvents, beginning with acetonitrile..."). A copy of this article is attached for convenient reference. Therefore, in light of the existing knowledge of the art, an ordinarily skilled artisan apprised of Applicant's disclosure would reasonably understand the claim terms "polar aprotic solvent", and that the claimed invention is not limited to acetonitrile. Accordingly, withdrawal of this ground of rejection is respectfully requested.

#### Rejection Under 35 U.S.C. § 103

Claims 1-5 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 4,604,463 to Miyasaka, et al. ("Miyasaka"). The reasons for the rejection are stated on page 3 of the Office Action. The rejection is respectfully traversed.

Initially, in order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation in the cited reference(s), or in the knowledge generally available to one of ordinary skill in the art, to make the asserted modification to achieve the claimed subject matter. See MPEP § 2143. As stated in MPEP § 2142, third paragraph:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (Emphasis added).

It is asserted in the Office Action that Miyasaka meets all the limitations of instant claims except that Miyasaka uses pyridine instead of instant 4-dimethylaminopyridine in the condensation reaction. It is further asserted that the reactants and products are identical in the process of Miyasaka and that, in the absence of any unexpected results, it would have been obvious to use substituted pyridine instead of pyridine in the condensation process for preparing 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxy-camptothecin. Applicant respectfully disagrees with these assertions.

According to Miyasaka (column 25, Example 28), 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin is prepared as follows:

7-ethyl-10-hydroxycamptothecin (790 mg, 2,01 mmole) and 1-chlorcarbonyl-4-piperidinopiperidine (910 mg, 3,95 mmole) are dissolved in anhydrous pyridine (50 ml), and the mixture was stirred for 1 hour at room temperature.

The reaction mixture is evaporated to dryness in *vacuo* and the residue was dissolved in CHCl<sub>3</sub> (200 ml).

The solution is washed successively with 7% aqueous solution of NaHCO<sub>3</sub> (200 ml), a saturated aqueous solution NaCl, and the CHCl<sub>3</sub> layer was dried with MgSO<sub>4</sub>, filtered, and evaporated in *vacuo*.

The residual material is decolorized by passing it through a short silica gel column whereby 1,11 g (94,8% in yield) of the title compound was obtained as a pale yellow mass which was recrystallized from ethanol (ca. 60 ml) to give colorless needles (750 mg, 63,5% in yield).

It ensues from the foregoing that the method described in Miyasaka affords a reaction mixture having to be treated to obtain a pure 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin with very sophisticated treatment process which, in turn, considerably decreases the yield of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin.

In contrast, the claimed method provides a reaction mixture that need not be treated in such a complicated manner. In fact, this mixture can be simply worked using only one treatment step to yield the pure 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin, which is washing with, for example, acetonitrile (see Example 1 of the present application). As a result, a yield of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin highly going over 90% is reached.

Applicant has also discovered that utilizing the system of polar aprotic solvent/4-dimethyl aminopyridine recited in claim 1 in combination with implementing the condensation of 7-ethyl-10-hydroxycamptothecin with 1-chlorocarbonyl-4-piperidinopiperidine result in a considerably higher yield of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin, which is the unexpected result of practicing the claimed method. Thus, it should be appreciated that achieving the claimed method requires more than the mere substitution of a substituted pyridine for pyridine advanced in the Office Action.

Accordingly, the methods recited in claims 1-5 are not rendered obvious nor suggested by Miyasaka since the reference fails to provide any details regarding both the replacement of pyridine with the system of polar aprotic solvent/4-dimethyl aminopyridine and the higher product yield resulting from this replacement. Thus, the skilled artisan would not have found any motivation in Miyasaka to substitute the system of the polar aprotic solvent and 4-dimethylaminopyridine for pyridine to result in the claimed method. Based on the foregoing reasons, claims 1-5 are believed to be patentable. Withdrawal of the rejection of claims 1-5 is respectfully requested.

Accordingly, the application and claims are believed to be in condition for allowance, and favorable action is respectfully requested.

If any issues remain, the Examiner is respectfully invited to contact the undersigned to advance the application to allowance. No new matter has been added.

Respectfully submitted,

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